



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/086,025	02/28/2002	Marc R. Anderson	286697-00005	7853

7590 09/28/2004

MacPherson Kwok Chen & Heid LLP
1762 Technology Drive
Suite 226
San Jose, CA 95110

EXAMINER

SODERQUIST, ARLEN

ART UNIT	PAPER NUMBER
----------	--------------

1743

DATE MAILED: 09/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,025	ANDERSON ET AL.	
	Examiner	Art Unit	
	Arlen Soderquist	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 July 2004 and 20 April 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 109-124 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 109-124 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1743

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 8, 2004 has been entered.

2. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 106-121 been renumbered 109-124 as per the attached interview summary.

3. The amendment filed April 20, 2004 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the changes to the paragraph beginning on page 1, line 19 removed references to a related patent and application along with their incorporation by reference; the change to the paragraph beginning on page 2, line 13 removed an admission that the preferred embodiment of the invention uses the method known as Speciated Isotope Dilution Mass Spectrometry (SIDMS); the change to the paragraph beginning on page 5, line 29 again removes a reference/admission that patented techniques are used in the invention; the deletion of paragraphs beginning on page 18, line 31 and page 19, line 11 remove information related to the SIDMS technique; and the change to the paragraph beginning on page 19, line 17 broadens the disclosure by changing a positive recitation that the apparatus uses the SIDMS method to the apparatus may use the broader IDMS method.

Applicant is required to cancel the new matter in the reply to this Office Action.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 114, 116-117 and 124 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification in the discussion of figure 6, the dilution modules, contains a specific example in which each successive dilution changes the spike concentration by about 30 times. This does not provide sufficient basis to specifically claim a range of possible dilutions for each module as found in the claim 114. The first paragraph of page 32 of the instant specification teaches that the arrangement and sizing of syringes, as well as the distance of driving plungers and the rate of plunger travel, is such that the dilutions provided the specified concentrations. This does not support specifically claiming only one of the three things listed as the means to achieve the dilution as in claim 116. Claim 124 has the same problem as claim 114 in that a single example is given in which each successive dilution has about the same rate or ratio of dilution: about 30 times.

6. Claims 109-117 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: at least one spike source to provide antecedent basis for the limitation found in renumbered claim 118 (former claim 115). The device cannot function consistent with its intended use without a spike source.

7. Claims 109-124 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 109, "the components" does not have antecedent basis. In claim 109 the spike dilution apparatus, mixer, atmospheric pressure ionizer and mass spectrometer are all "configurable to" perform an operation of some sort. It is not clear if this language is attempting to cover a system having these components that is capable of being modified but not yet configured to perform the respective functions or if the language actually requires the system to have the respective components in a configuration that allows the components to function as stated. The control system of claim 109 appears to indicate that the other system components can be configured in a manner different from that stated since the control system is adapted to automatically configure the components to perform the stated

Art Unit: 1743

functions – they do not always have that configuration. In claim 110, it appears that the sample extraction apparatus should be required to deliver or transfer the extracted sample to the mixer of claim 109. Claims 113, 116 118 also suffer from the “configurable to” problem of claim 109. In claim 114, it is not clear if the dilutions are a percentage (30% less each dilution), a multiple (30 times less each dilution) a specific change in concentration (30 ppb less each dilution) or if each dilution sub-module performs a certain number of dilutions. For examining purposes, the claim will be examined using the example in the specification in which each successive dilution causes the concentration to change by about 30 times. In claim 115 it is not clear if applicant is trying to claim a specific change in the concentration after the last dilution relative to the initial concentration or if the “may be six orders of magnitude” is only a possibility and applicant intends the claim to cover all possible situations with the language. If the latter case is true then the claim fails to further limit the claim from which it depends. In claim 119, it is not clear if the estimate is required to be anywhere near the concentration of the analyte or if the estimate includes situations where the concentration is known by some other method. In claim 124 it is not clear what is appropriate or not appropriate in selecting the dilution achieved in each successive dilution.

8. Claims 119-124 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: that the spike concentration is about the same concentration as the analyte in the sample. in the discussion of the basis for claim 119 (old number 116), applicant points to the paragraph starting on page 30, line 19. Two sentences of that paragraph from page 30, lines 22-27 are reproduced below.

“It is necessary in embodiments of the invention that the relative concentration of the spike for any specie for which monitoring is accomplished be in the same general range as the expected concentration in the sample. If the spike concentration is either much too high or much too low, then the mass spectrometer will not be able to provide a ratio of isotopes with adequate resolution to determine the sample concentration.”

It is clear from this section that a specific relationship between the spike concentration and the concentration of the monitored specie in the sample exists for the method to provide a ratio with adequate resolution as in claim 121 (old claim 118). Thus this condition is required or necessary for the method to perform its intended purpose.

Art Unit: 1743

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 109-112 and 118-122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marchante-Gayon, Rottmann or Viczian in view of Maxwell (newly cited and applied) or Köster (US 6,730,517 newly cited and applied) and Kingston (US 5,414,259 or WO 99/39198), Dureault and Multala.

In the paper Marchante-Gayon presents a study of random and systematic errors for the determination of molybdenum by inductively coupled plasma mass spectrometry using online isotope dilution analysis. Reverse isotope dilution analysis was applied for the determination of the concentration of a ⁹⁵Mo enriched spike and the procedure was automated using an auto sampler where natural Mo standards and samples were alternatively mixed online with the spike solution. A new equation is proposed for the online mixing of samples and spike using the autosampler. The measurement of a natural Mo standard between the samples makes possible to perform isotope dilution analysis referring the results to the natural Mo standard regardless of the concentration of the spike. The effects of both systematic and random errors were examined and the error theory was applied for the accurate determination of Mo in biological materials by ID-ICP-MS. On page 86 in the second and third paragraphs two solutions having molybdenum at concentrations of about 1 µg/g were produced by diluting a first solution having a higher concentration. The second solution is the enriched isotopic spike solution. The last paragraph of the page teaches this spike added online with the help of an autosampler, a two channel pump

Art Unit: 1743

and a T piece placed before the nebulizer. Marchante-Gayon does not teach all of the system components.

In the paper Rottmann presents the development of an online isotope dilution technique with HPLC/ICP-MS for the accurate determination of elemental species. An online isotope dilution technique was developed for use with a HPLC system (HPLC) coupled to an inductively coupled plasma mass spectrometer (ICP-MS). With this method it is possible to characterize elemental species at low concentration levels and to quantify them accurately. The possibilities of this method are shown using the samples of the determination of the interactions of different molecular weight fractions of dissolved organic matter (DOM) with copper and molybdenum in a natural water sample. Page 3711 teaches that the spike solution is prepared by diluting a commercially available standard solution or stock solutions prepared from isotopically enriched solids. The last full paragraph of the page teaches mixing the spike with the sample online through a Y-junction. Rottmann does not teach all of the system components.

In the paper Viczian teaches on-line isotope dilution and sample dilution by flow injection and inductively coupled plasma mass spectrometry. A systematic investigation was made to demonstrate the applicability of a flow injection system for online isotope dilution and online sample dilution, as obtained by merging the sample solution with the spike solution or with the diluent, respectively. The effect of the sample to spike ratio on the precision and accuracy was examined, and the advantages and limitations of the proposed technique are demonstrated. A plurality of enriched spike concentrations is taught on page 127 in the second paragraph of the "On-line Isotope Dilution and Spike to Sample Ratio" heading. Viczian does not teach all of the system components.

In the abstract Maxwell teaches an automated spike preparation system for isotope dilution mass spectrometry. Isotope Dilution Mass Spectrometry (IDMS) is a method frequently employed to measure dissolved, irradiated nuclear materials. An automated spike preparation system was developed at the Savannah River Site (SRS) to dispense spikes for use in IDMS analytical methods. The new system employs a high precision SMI Model 300 Unipump dispenser interfaced with an electronic balance and a portable Epson HX-20 notebook computer to automate spike preparation. Using the computer to collect duplicate net weights on a predetermined number of spike containers, dispensing accuracy is confirmed by a statistically-

Art Unit: 1743

based sampling plan. The density of the spike solution, the volume setting on the Unipump dispenser, and the calculated net weights of the spikes, the average weight of the spikes are calculated along with the observed variance estimate. If the observed variance control limits, the spikes are released and treated as having equal quantities of the spiked isotope within the calculated uncertainty estimate. This feature eliminates a whole layer of bookkeeping and the need to track individual spike containers and their individual quantities of the spiked isotope.

In the patent Köster teaches an automated process line in which fully a fully automated modular analysis system integrates instrumentation to permit analysis of biopolymer samples, such as nucleic acids, proteins, peptides and carbohydrates. The system integrates analytical methods of detection and analysis, such as mass spectrometry, radiolabeling, mass tags, chemical tags, fluorescence and chemiluminescence, with robotic technology and automated chemical reaction systems to provide a high-throughput, accurate automated system for high throughput analyses. Column 1, lines 25-40, teach that current methods of testing typically employ multiple instruments for preparing and analyzing samples and involve multiple manual handling steps and transfers. Such procedures are labor-intensive, time-consuming, and costly and they are susceptible to human error, sample contamination, and loss. After samples have been prepared, they can be subjected to testing procedures that produce data for analysis. Conventional testing procedures often must be performed by an individual laboratory technician, one sample at a time. Laboratory technicians are typically individuals who are most likely trained to operate only a single instrument. Automation will reduce the number of personnel and training necessary to carry out the research. Reliable and accurate automated process and analysis tools are necessary for the benefits of recent scientific discoveries to be fully achieved. Column 2 gives some of the advantages of automation and give a summary of the device and method. Columns 9-11 discuss the automated process line including the addition of mass tags (isotopic spikes).

In the published application Kingston teaches speciated isotope dilution mass spectrometry of reactive species. Speciated isotope dilution measurement of reactive species by spiking stable isotope to convert to speciated enriched isotope corresponding to species to be measured. The method is carried out by providing at least one predetermined stable isotope. The sample is spiked by an isotopic spike prepared by converting the stable isotope to a speciated enriched isotope corresponding to the species to be measured in the sample. The

Art Unit: 1743

isotopic spiked species are equilibrated with the species to be measured. At least a portion of the species is separated from the sample and isotope ratio determination is carried out for each species to be measured. The species concentration is mathematically deconvoluted, using given mathematical formulas, while correcting for species conversion and/or incomplete separation. To determine a species of interest in environmental, biological, pharmaceutical and industrial samples and standard reference materials, e.g. Cr (III) a trace element essential for human health and Cr (VI) poisonous to most animals. An accurate quantification of the species of interest is ensured in spite of incomplete extraction, conversion, solubility, separation, isolation or degradation of species. The method facilitates correction for incomplete isolation of species through the use of a tag, which joins the isotope spike with the species to be measured.

In the patent Kingston teaches species measurement using enriched isotope spikes of same speciated form - involves using species ratio to measure, equilibrate, separate and subsequently determine the species concentration by dilution mass spectrometry. Method of isotope dilution measurement of a sample comprises: (a) providing at least one predetermined, stable isotope; (b) converting the isotope to a speciated enriched isotope corresponding to the species to be measured in the sample; (c) spiking the sample containing the species to be measured; (d) equilibrating the spiked species with the species to be measured; and (e) separating all the species from the sample and determining the concentration of the species to be measured by employing isotopic element species ratios. Time-resolution chromatography may be employed to effect the separation and a mass spectrometer may be employed in the isotope dilution measurements. A determination as to whether isotope conversion has occurred is made. Species measurement using enriched isotope spikes of same speciated form. The species ratio is employed to measure, equilibrate, separate and subsequently determine the species concentration by dilution mass spectrometry.

In the published application Dureault teaches an automatic sampling, diluting and analyzing module. The module has 1st and 2nd sections containing eight-way valves, which are operable to sample test liquid, add diluents and reagent prior to analysis. Typically the 1st section samples the test liquid using a syringe pump to supply a loop. Syringe sucks up diluent and then scavenges liquid from the loop for dilution and supply to a 2nd loop. Another syringe scavenges the now diluted sample from the 2nd loop and sucks up reagent and diluent and then

Art Unit: 1743

delivers the resulting sample/reagent/diluent mixture to an analyzer. Utility is in analyzing hydrazine in solutions used in nuclear fuel reprocessing using dimethylaminobenzaldehyde reagent.

In the paper Multala teaches computer controlled start-up and monitoring system for a pilot-plant distillation column including an on-line quadrupole process analyzer. The start-up-2/75 distillation control system presented is based on a known the start-up-1/75 system reported by K.K. Salminen and A. Halmu (1977). System enhancements are on-line, quadrupole, mass-spectrometric process analyzer and a reporting program to print out state reports of the distillation column in real time. Six sample points in the distillation process are analyzed continuously by the on-line control system. The sampling rate is 30 s and the analyzing rate ~1 s. A relative accuracy of 2% was achieved with binary water-ethanol mixture. A state report is printed, normally, every 3 minutes, including concentrations, flows, temperatures, and mass balances. The system can be applied to experimental research of transient responses and distillation process dynamics.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate means to automatically prepare the spike as taught by Maxwell or Köster through dilution as taught by Marchante-Gayson, Rottmann or Viczian because of the advantages for automation taught by Köster or generally known in the field. It should be noted that claims 109 and 119 do not require the connection of the analyzer to the process solution. It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the various apparatus of Kingston, Dureault and Multala into the device and methods taught by Marchante-Gayson, Rottmann or Viczian because of the automation advantages taught by Kingston, Dureault and Multala and the recognition that the apparatus of Marchante-Gayson, Rottmann or Viczian can perform the isotope dilution analysis on a variety of samples including industrial as taught by Kingston.

11. Applicant's arguments filed April 20, 2004 have been fully considered but they are not persuasive. First the new grounds of rejection add references showing the automation of spike dilution. Additionally there are several issues with clarity or new matter. Examiner would also like to point out that the primary references all teach dilution of a spiking solution to arrive at the spiking solution used in the apparatus and methods. This leads directly into the automation of

Art Unit: 1743

that process in view of the Maxwell and Köster references. Examiner also points out that there is no direct connection between the apparatus claimed in claim 109 and a process solution. Thus one could carry a sample to the device of claim 109. Even in claim 110 the scope of the language is capable of covering an autosampler. In response to applicant's argument that none of the references teach or suggest the advantageous combination of elements relative to the computerized control and management system, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Examiner notes that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981) and *In re Sneed*, 218 USPQ 385, 389 (Fed. Cir. 1983). Additionally relative to the advantages of examiner being different from those of applicant, each of the Kingston, Dureault and Multala references teach advantages relative to the automation of analysis. With two of the references, Dureault and Multala the advantages are with respect to automates extraction (sampling) for analysis of process fluids and in at least the Kingston reference, this automation is related to isotopic specie determination. Relative to the obviousness type double patenting rejection, it has been withdrawn for now but will be considered in the future relative to the claims of applications 10/004,627 and 10/094,394.

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The additionally cited art relates to online dilution and isotopic dilution.

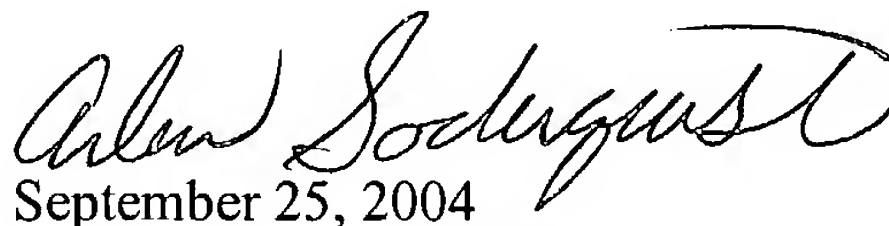
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose current telephone number is (571) 272-1265 as a result of the examiner moving to the new USPTO location. The examiner's schedule is variable between the hours of about 5:30 AM to about 5:00 PM on Monday through Thursday and alternate Fridays.

A general phone number for the organization to which this application is assigned is (571) 272-1700. The fax phone number to file official papers for this application or proceeding is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

Art Unit: 1743

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



September 25, 2004

ARLEN SODERQUIST
PRIMARY EXAMINER